ADELLE DAVIS

AND

ATHEROSCLEROSIS:

An In-Depth Critique

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August, 1974

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THE STYLE OF ADELLE DAVIS

Adelle Davis' best-selling books, <u>Let's Eat Right to Keep Fit</u>,
<u>Let's Cook It Right</u>, <u>Let's Have Healthy Children</u>, and <u>Let's Get Well</u>
have acquired a large following over the past decade and have influenced
the dietary habits of many Americans. What makes Miss Davis' proposals
rather unique in the current onslaught of food fad literature is that she
claims that all her statements stem from medical evidence found in the
scientific literature. In fact, Adelle Davis' credentials are those of a
scientist. According to the frontpiece of the book <u>Let's Get Well</u>, she
has "Studied at Purdue University, graduated from the University of
California at Berkely, and took postgraduate work at Columbia University
and the University of California at Los Angeles before receiving her Master
of Science degree in biochemistry from the University of Southern California
Medical School." She has written three of her books with very little
attempt at comprehensive documentation. However, one book, <u>Let's Get Well</u>,
is thoroughly referenced. This rather small book of some 350 pages has
approximately 2300 references -- almost every sentence has at least one
reference.

Adelle Davis has the ability to set forth her ideas in a very con-
vincing, alluring way. She combines extraordinary case histories from
her own personal experience with "facts" which she "quotes" from respect-
able journals. She describes the basics of biochemistry and physiology

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in such a way as to lend support to her nutritional claims. Her rather ingenious exposition leaves the reader incredulous that such obvious, documented interrelationships between nutrition, biochemistry, and physiology are not known to all physicians as well.

Since Miss Davis did take the effort to reference so thoroughly one of her books, this writer felt it would be an interesting challenge to check her references and determine exactly how well her story is in line with the literature she quotes. If the basic thrust of her claims are supported by sound research, then perhaps it is time to take another careful fook at the medical literature and try to establish a new and perhaps more fundamental role for nutrition in treating disease. If, on the other hand, her statements are not supported by the references she quotes, then it would be interesting to see just where and to what extent she deviates from the rational to the irrational.

Let's Get Well is divided into 34 chapters. Each chapter deals with a different disease and describes the role which nutrition might play in the etiology and treatment. Some topics covered are heart disease, ulcers, diabetes, arthritis, infections, allergies, gout, and anemia. This report deals with chapter five entitled "Those 'Cholesterol' Problems," which deals with the role of nutrition in cholesterol metabolism and atherosclerosis. Each of the references pertinent to this chapter were examined, and the extent to which each reference documented her claims was determined.

This chapter was chosen primarily because atherosclerosis is a disease process which concerns a large number of Americans. Also, Adelle Davis' assertions that weight loss and reducing cholesterol intake are not important considerations in lowering serum cholesterol run counter to most current medical opinion and might possibly be considered dangerous to those with atherosclerosis. Thus, whether or not Miss Davis' claims on this subject are valid may have a direct bearing on the health of those who take her seriously.

THE NATURE OF HER REFERENCES

One hundred seventy (170) references were quoted in support of

chapter five. All but three were reviewed. Of these three, one was a

book (<u>Alpha-Tocopherol in Cardiovascular Disease</u>, by E.V. Shute and

W.E. Shute - reference 111) which was currently unavailable to this

writer, and two were misreferenced and could not be found (Gross, K.L.,

et. Al., N.Y. State J. Med. 30;2683, 1950-reference 39, and Barnett, L.B.,

Clin, Physiol. 1;26, 1959-reference 89). Three references were repeated

twice - thus there were in total 167 references (165 correctly cited).

The vast majority of footnotes in chapter five were therefore correctly

referenced and were easily obtainable.

As each article quoted by Miss Davis was read, it was assigned a

number based on its relevance to the statement which it was used to

support. This system of grading, although arbitrary, was intended to

give some index of the quality of the referencing. The following values

were thus assigned to each reference quoted:

0   Article does not relate whatsoever to statement
     (or statement contradicts article's intent)

1   Article relates to statement but is taken out of context
     or is misconstrued

2   Article relates to statement but is not totally supportive
     (poor choice of reference)

3   Article relates to statement and provides evidence and/or
     confirmation

Values 0 and 1 indicate that the author of the article probably

would not agree with Adelle's statement (based on the material presented

in this article), while values 2 and 3 indicate that the author probably

would agree with her statement.

Of 201 footnotes in chapter five, 112 were found to have no bearing

to the statement where they were cited, and thus received a zero score.

Only 30 received a score of three. Fifty received a number 1, and nine

scored a two. These figures are tabulated in the table.

Score	# of references receiving this value
3	30
2	9
1	50
0	112

Average score for each reference   0.79

Thus, the majority of Miss Davis' assertions are not supported by

the articles which she cites for confirmation. However, this kind of

statistical information must be treated cautiously, since this grading

system is rather arbitrary. This writer will soon analyze in a similar

fashion the references from another, more reputable source, to see if

an average score of close to 3 is obtained.

To give an idea of the type of careless referencing Miss Davis

employs, several examples will be given below.

> Miss Davis states that "Countless experiments with healthy
> volunteers, survivors of heart attacks, persons in prisons and
> mental institutions,[6,7] and innumerable animals show that when
> fatty substances are being deposited in the arterial walls, the
> blood cholesterol is invariably high and in abnormally large

particles; and that the fat in the blood which is combined with phosphorous, known as the phospholipids, or lecithin, is too low." (Let's Get Well - p. 49)

References 6 and 7 were entitled respectively, "Effect on Serum-Cholesterol Level of Replacement of Dietary Milk Fat by Soybean Oil," and "The Influence of Partially Hydrogenated Dietary Fats on Serum Cholesterol Levels." Both articles were concerned only with the lowering of serum cholesterol through the use of different levels of saturated fats in the diet. The only relevance they had to Miss Davis' statement was that subjects for both studies were volunteers from mental institutions.

Occasionally, Adelle Davis misunderstood an article which she quoted. An example of this is as follows:

> If the diet furnished sufficient linoleic acid, the other two essential acids (linolenic acid and arachidonic acid) can be synthesized from it provided a bevy of vitamins and minerals are also present,[13,14] but several of these nutrients may be undersupplied. (Let's Get Well, p. 50)

Reference 13 is concerned with the possible role of essential fatty acid deficiency in producing myocardial infarction in rats fed an atherogenic diet. This has nothing to do with the above sentence. Reference 14 is an article from the Journal of Biological Chemistry entitled "Conversion of γ-linolenic to arachidonic acid." Here evidence is presented which suggests that γ-linolenic acid (18:3ω6) is an intermediate in the synthesis of arachidonic from linoleic acid. As Adelle is undoubtedly referring to linolenic acid (18:3ω3) here, which cannot be synthesized from linoleic acid, her statement is unsupported.

A certain amount of the poor referencing score derived earlier is certainly due to careless editing and collection of reference material. For example, Miss Davis says:

> Animals most resistent to experimental atherosclerosis are those with the greatest ability to produce lecithin.[30] (p.51)

Reference 30 is concerned with the effect of intravenous administration of Tween 80 to rabbits on the prevention of atherosclerosis and has nothing to do with her statement. However, reference 34 is entitled "Biochemical studies in relation to comparative susceptibility to experimental atherosclerosis" and describes the relative ability of rat, guinea pig and chick. liver slices to convert labelled ethanolamine to phosphatidyl choline. This was then related to their resistance to develop atherosclerosis. Since this article is used inaccurately to support a statement concerning low blood lecithin in atherosclerosis patients, it could just as easily been used to better document the above sentence.

This type of carelessness occurs repeatedly. For example, she states:

> Moreover, when a solid fat in an experimental diet is partly
> or completely replaced by a vegetable oil, the blood cholesterol
> and fat decrease as their utilization improves; but if the
> vegetable oil is gradually hydrogenated and fed to groups of
> animals, the blood cholesterol rises with each increase in
> hydrogenation.[51] (p. 52)

Reference 51 is concerned with the cholesterol-lowering effect of different fractions of sunflower seed oil. However, reference 7, although the work is done in humans, is concerned with the study of this type of hydrogenation effect on serum cholesterol levels.

Therefore, it can bee seen that although a large percentage of references quoted do not relate to their appropriate subject matter, this does not necessarily mean that the statement is incorrect. In fact, a supportive reference may even be present among the other 166 cited for the chapter. Adelle Davis' arbitrary handling of her footnotes results in many of her statements, even if partially true, going unsupported. This will become even more apparent later.

However, to convey some idea of the extent to which she provides support for her own theories, a brief review of the chapter and references will be presented.

THE CHAPTER IN REVIEW

THOSE CHOLESTEROL PROBLEMS

Introduction

Little is referenced in this section. Reference 1 is an early
review article of the role of lipids in atherosclerosis, and does show
the similarity upon chemical analysis between plasma lipids and aortic
lipid deposits. Reference 3 does not imply that atherosclerosis is at all
responsible for hypertension, as Miss Davis seems to suggest. Reference 4
is concerned with the effect of dietary levels of protein on hypercholesteremia
in the rat, but part of this study does indicate that rats made hypertensive
through the administration of desoxycorticosterone acetate do show an in-
creased incidence of atherosclerosis. This last reference is character-
istic of Adelle Davis' tendency to take an extremely specific study and
construe it as providing general evidence for a related point.

Atherosclerosis is Reversable

Many statements are made here, yet there are very few references.
Reference 9 is a general review of the relationship between cholesterol
metabolism and atherosclerosis, and does provide general support for
Adelle's partially correct statement. According to this article, the
liver is the source of almost all endogenously derived plasma cholesterol.
Exogenous cholesterol reaches the blood in the form of chylomicrons from
the lymph.

The last sentence, needless to say, concerning cholesterol metabolism
is unsupported, namely "It (cholesterol) enters the small intestine with
bile, passes into the blood, and, if all nutrients are generously supplied,
is eventually broken down by the cells into carbon dioxide and water." (p. 49)

Saturated and Unsaturated Fats

The first paragraph is relatively straightforward. References 10
through 12 all indicate that the percentage of unsaturated fatty acids
in serum of control subjects is higher than in that of subjects with a
history of heart disease. Reference 10 also shows that controls had a
slightly higher percentage of polyunsaturated fatty acids in their storage
fat depots. In these studies, however, the differences between the coronary
heart disease groups and the control groups were never as large as
Miss Davis suggests.

The last paragraph contains many unreferenced sentences. One such
statement is "Though many factors are involved, when fats cannot be
burned readily by the tissues, they are dammed up in the blood." Taken
in context, this sentence implies that a prime reason why this improper
utilization occurs is due to a deficiency of linoleic, linolenic, and
arachidonic acid, which will occur if the diet is lacking in linoleic
acid and "a bevy of vitamins and minerals." She makes no attempt to
document this rather liberal interpretation of lipid metabolism.

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The Importance of Lecithin, or Phospholipids

Most of the references cited in this section do not lend support to the appropriate statements. Indeed, most are not even relevant to the subject matter.

Her first two paragraphs are concerned with the metabolism of lecithin (her inclusive name for all phospholipids). Of references 15 to 26, only six provide some support for her assertions. Her statement "It (lecithin) aids in the transportation of fats, helps the cells to remove fats and cholesterol from the blood and to utilize them; and increases the production of bile acids made from cholesterol, thereby reducing the amount in the blood"[15-18] is unsupported; in fact, references 17 and 18 point out how little is known regarding the lipotropic effect of choline.

All atherosclerosis is not characterized by a decrease in serum lecithin, as Adelle proposes. While serum cholesterol appears to increase, so does serum phospholipid.[9,10]

Adelle Davis claims that lecithin is helpful in curing experimental heart disease. Reference 28 is a study reported in 1935 in which rabbits were placed in dietary sub-groups of two each and were given varying amounts of cholesterol, lecithin, and vitamin D. This investigator found that even small amounts of lecithin (3 grains) given to cholesterol-fed rabbits prevented the usual vascular lesions. Reference 29 is a similar study in which 23 rabbits were divided into three groups. All were fed

150 mg. cholesterol daily. Two groups were also given one and five

grams of soya lecithin (20% lecithin) per day. After four months, ather-

osclerotic lesions of the aorta were seen in four of the fifteen rabbits

fed lecithin, but they were present in seven of the eight control rabbits.

Both of these studies suffer from a very small sample. Reference 30

demonstrates that intravenous injections of a detergent (high in phos-

pholipids) in rabbits will raise the plasma cholesterol and phospho-

lipid (with a net rise in the phospholipid/cholesterol ratio), yet will

result in significantly less atherosclerosis compared with controls.

These last three experiments all provide support for Adelle's claims,

although the last two are not relevant to the footnoted statements.

References 31-38 bear no direct relevance and do not accurately

document statements in the next two paragraphs. The only exception is

reference 35, which is an excellent study similar to that described

above (reference 30). Intermittent intravenous infusions of phosphatide

in previously hypercholesteremic rabbits appeared to decrease the amount

of atherosclerotic infiltration compared with dextrose infused control

animals. Although no mention is made of a bile duct ligation, as in

Miss Davis' book, this study does indicate that "fatty deposits in the

arterial walls are quickly removed."

Adelle states that "Many physicians have successfully reduced blood

cholesterol with lecithin."[38-40] References 38-47 should be concerned

with the clinical use of lecithin to reduce serum cholesterol and improve

the symptoms of atherosclerosis. Only one, #44, is relevant. The least related article of these is #42, which is entitled "Research and Educational Progress in Nutrition." Here, C.G. King discusses, among other topics, the importance of fighting food faddists through the media. Reference #44, called "Serum Cholesterol Reduction with Lecithin" by L. M. Morrison, reports that of 15 hypercholesteremic patients on a low-fat diet and 36 grams of soya lecithin per day, twelve showed marked reductions of serum cholesterol, including one patient who dropped from 1012 mg% to 186 mg% in three months. The average reduction was 115 mg% (30%). Morrison claims these results are statistically significant. This uncontrolled study with a small sample is the only support she presents, despite the large number of references cited.

The Need for Vegetable Oil

Adelle Davis' statement that "The more arachidonic acid that there is in the blood of animals, the more resistant they are to atherosclerosis"[50] is supported by an interesting paper which demonstrates that arachidonate levels in serum correlate extremely well with species susceptibility to develop atherosclerosis in the rat, dog, man, goose, chicken, rabbit, pig, and guinea pig. The authors speculate that an essential fatty acid deficiency might play a role in the etiology of atherosclerosis, however, they leave open the possibility that arachidonate levels in serum cholesterol esters may be characteristic of each species.

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Adelle Davis' next statement, that of the administration of essential fatty acids to increase low blood lecithin is not supported by her references.

References 52, 53, 55, and 56 are concerned with the action of poly-unsaturated fatty acids on lowering serum cholesterol and on increasing the amount of bile salts excreted in the feces. No mention is made of their effect on cholesterol absorption. References 54, 57, and 58 do not relate to the effect of fatty acids on cholesterol metabolism at all.

Inositol and Choline are Essential

Reference 65 indicates that a complete choline deficiency in the rat will decrease serum phospholipid levels, and, while references 66 and 67 aren't pertinent, #68 does demonstrate the production of ather-omatous changes in the aorta, carotid and coronary arteries in 25 of 116 rats fed a choline deficient diet for 216 days. The reader of Miss Davis is probably left with a misconception here, since she hints that all rats developed these lesions.

Adelle Davis mentions that methionine can lower blood cholesterol. In the mouse, rat (reference 71), and in the monkey (reference 73, 74) blood cholesterol has been shown to drop when methionine is added to a sulfur amino acid deficient diet. Miss Davis does not mention that a specific methionine deficiency state is necessary first to induce a hypercholesteremia which is then lowered upon methionine supplementation.

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Miss Davis claims that choline will lower serum cholesterol. T.D. Labecki (reference 75) administered two grams of choline, and one gram of methionine, and over 600 mg of inositol to a control group and to a group with previous myocardial infarction. He observed a reduced fasting chylomicron count in both groups, a drop of serum cholesterol of borderline significance in the infarct group, and an increase in alpha to beta lipoprotein ratio in this group. However, the blood cholesterol never dropped to normal, contrary to Miss Davis. Rawls et. al. (reference 77) administered a preparation of approximately .75 gram methionine, .60 gram inositol, 2.0 gram choline, and 15μg. vitamin B_{12} to 334 patients and found no effect of the drug on serum cholesterol or on the cholesterol-phospholipid ration, but found a decrease in the chylomicron count. The authors suggest that a relationship between hyperchylomicronemia and atherosclerosis might exist, and thus a 'lipotropic' supplementation might be beneficial to certain patients. References 76, 78, and 79 are not related to the question of the alteration of serum cholesterol and phospho-lipid with choline.

Thus, Adelle Davis does not provide support for the idea that the supplementation of choline in the diet will lower serum cholesterol and increase the phospholipid to cholesterol ratio in the serum.

Vitamin B_6 and Magnesium

Adelle Davis claims that vitamin B_6 is essential for the production of lecithin and in this way plays a role in the prevention of athero-sclerosis. Although reference 80 is concerned only with the effect of

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pyridoxine on essential fatty acid metabolism, Pilgeram (reference 34) does suggest that vitamin B_6 is necessary for the decarboxylation of serine to form ethanolamine (actually phosphatidyl serine is converted to phosphatidyl ethanolamine) and thus may play a role in the biosynthesis of phosphatidyl choline. Reference 81 does not implicate magnesium in these conversions.

References 82 and 83 do report the development of arteriosclerotic lesions in pyridoxine deficient dogs and monkeys, however, no mention of serum cholesterol and phospholipid is made.

As she has mentioned before, Miss Davis believes that vitamin B_6, choline, and inositol supplementation "have been partially effective in reducing blood cholesterol."[84,85] When a brain extract (rich in cerebrosides and lecithin) was administered to 70 patients, a definite hypocholesteremic response was noted (reference 85). However, the authors attributed this to the ability of the extract to bind with cholesterol and bile acids and prevent intestinal absorption. They did not suggest that B vitamins might be responsible. Reference 84 is concerned with the experimental production of gall stones in the rat and thus is not related.

References 86 through 89 should report the effect of magnesium therapy on heart disease patients. In fact, only reference 88 is concerned with this. Here Malkiel-Shapiro et. al. report the clinical improvement of twenty out of twenty-two coronary heart disease patients

following intra-muscular injections of magnesium sulphate. Trials were uncontrolled. They also indicate a significant decrease in the percentage of beta lipoproteins in the serum of these patients. No explanation as to why this therapy might be effective is presented.

Reference 90 does indicate that cholesterol feeding might increase the magnesium requirement in the dog. In this paper there is cited a study by Vitalle et. al. (Am. J. Clin. Nutr. 7, 13, 1959) where "the magnesium requirement of the young rat was increased fourfold by feeding an atherogenic diet containing 20% fat, one per cent cholesterol, and 0.3% cholic acid." The quote of a 16 fold increase is thus incorrect.

Reference 91 is concerned with the effect of magnesium deficiency in rats on oxidative phosphorylation and is not at all relevant. Her statement "Even after the arteries were severely plugged with fatty deposits, adequate magnesium caused the blood cholesterol to drop to normal and the arteries to become healthy," is totally unsupported.

Vitamin E Has Much to Offer

References 96, 99, and 100 are all related to the work of T. Gillman et. al., who feels that intimal scarring in arteries at an early age may play a major role in the etiology of atherosclerosis. Since Adelle Davis believes that vitamin E can "dissolve" such scars (not supported in this chapter), she enthusiastically recommends it.

Vitamin E is shown in this section to reduce the hypercholesteremia produced by deficiency states in guinea pigs and rabbits (reference 102),

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reduce anoxia due to high altitudes in the rabbit (reference 105), lower

the oxygen consumption of dystrophic (vitamin E deficient) rabbit and

hamster muscles (references 104, 107), and lower the basal metabolic rate

of the rat (when administered in a huge parenteral dose in the form of

alpha-tocopherol phosphate, reference 106). None of these studies pro-

vide relevant evidence that vitamin E may in any way favorably affect

the patient with atherosclerosis. Reference 111 was unavailable, while

reference 112, by S. Tolgyes and E. Shute, report several case histories

where large doses of vitamin E were successfully used in the treatment

of small areas of gangrene. No mention is made concerning cardiovascular

heart disease or the pain of angina.

Other Nutritional Influences

The references Miss Davis employs in her paragraph concerning the

relationship between sugar and atherosclerosis generally support the

statements for which they are cited. The only notable exception is

reference 116, which reported the effect of varying carbohydrate intake

in rats on hepatic lipid content, and was unrelated to sugar intake and

blood essential fatty acid composition. However, the direct connection

which Miss Davis infers to exist between sugar consumption and athero-

sclerosis is not suggested by any of these references, save for a short

report by A. M. Cohen (reference 114) who insists that the increased

sugar consumption of Yemenite Jews who have migrated to Israel is

responsible for their increased prevalence of atherosclerosis. Reference 117, for example, which details the changes in retail market food supplies over the past 70 years in relation to the incidence of coronary heart disease, even suggests that sugar consumption in this country has leveled off since 1927, while coronary heart disease incidence rates have continued to increase.

In this section, Miss Davis reports that many dietary supplements may reduce high serum cholesterol and improve the prognosis of atherosclerosis. Pectin, for example, in reference 120, is shown to lower the hypercholesteremia in cholesterol fed rats. No explanation is given for this effect. For the effect of megadoses of vitamin B_{12} on cholesterol metabolism, Adelle Davis cites two references, one of which, reported in Nutrition Reviews, is simply a review of the other. The original article by Nath et. al. (reference 120) reports a well-controlled study where $5 \mu g/100$ grams body weight of vitamin B_{12} increased the excretion of bile acids and lowered serum cholesterol in rats fed a hydrogenated-fat enriched diet.

References 123-125 report the effect of huge doses of vitamin A acetate (100,00-180,000 IU daily) on serum cholesterol in adult patients. These studies are very poorly controlled and, while serum cholesterol was shown to decrease in coronary patients (reference 124, 125), statistical significance was not reported. No effect was found in patients with normal serum cholesterol.

References 127-129 deal with the effect of ascorbic acid on cholesterol metabolism. Reference 127, a study by C. G. King, reports that severely scorbutic guinea pigs, compared with normal animals, incorporate six times as much labelled carbon from acetate-1-C^{14} into cholesterol isolated from the adrenal glands. Miss Davis' interpretation of the study, that of vitamin C deficient monkeys producing cholesterol six times more rapidly than normal animals, is therefore somewhat liberal. Reference 128 indicates that large doses of ascorbic acid will depress serum cholesterol levels in rats and guinea pigs, and #129 reports Russian investigations which show that large doses of ascorbic acid may reduce serum cholesterol and prevalence of atherosclerosis in cholesterol fed rabbits. No mention is made of clinical studies in humans, nor is any mention made of a possible mode of action, both of which are reported by Miss Davis.

Although reference 135 documents Miss Davis' statement that iodine treatment prevented atherosclerosis in cholesterol fed rats, reference 134 is not pertinent to the statement preceding it. Reference 136 is an interesting Russian study by Pitel in which an iodide solution was given to patients with atherosclerosis. These patients showed a statistically significant decrease in serum cholesterol and beta lipoproteins, while serum phospholipids and alpha lipoproteins increased. A control group was included in this study, however data for this group was not reported. This omission is important, especially since all patients were put on a low-fat diet just prior to the study.

References 137-140 do not pertain to their corresponding statements.

Low-Fat and Low-Cholesterol Diets

References 141-143 provide general support for this first paragraph. There seems to be no question that low-fat diets reduce serum cholesterol (reference 142, 145). It is true, however, that a high carbohydrate diet will raise serum triglyceride levels (reference 142, 144) and thus L. Horlick (reference 143) recommends at least 14% of calories be supplied by unsaturated fat to avoid disturbances in lipid metabolism.

References 149 and 150 do not support the contention that low cholesterol diets result in high serum cholesterol, or that a high cholesterol intake decreased hepatic cholesterol production. In fact, reference 150 is entitled "Secretion rate of aldosterone in Normal Pregnancy," and clearly is not relevant to the subject in this chapter.

Reference 151 demonstrates that atherosclerosis can be produced in rabbits on a 20% coconut oil diet (without cholesterol). However, the remaining statements in this paragraph are unsupported. (Except for #154, which concerns the lipid composition of mayonnaise.) References 85, and 155 to 157 do not indicate that cholesterol ingestion will not increase serum cholesterol. In fact, reference 156 shows that 10 egg yolks, fed daily to two Bantu volunteers increased serum cholesterol from 76 to 110 mg% in less than a month.

Lowering Blood Cholesterol

Have Your Cholesterol Determined Annually

The few references found in these chapters are, with one exception, incorrectly cited. The exception is reference 167, which indicates that, in rabbits, atherosclerosis of the aorta does not recede after the termination of an atherogenic diet.

Summary and Conclusion

It can be seen that most of the footnoted statements in this chapter were poorly supported. There were, in addition, numerous assertions that were not documented at all. The conclusion which can be drawn is that Adelle Davis does not seriously back up her claims. While some convincing studies are cited concerning the effect of nutrition on cholesterol metabolism in animals (particularly vitamins C and B_{12}) no well designed studies with convincing results are reported in humans.

Based on this short review of the chapter "Those Cholesterol Problems," and the references cited, it is tempting to dismiss most of Adelle Davis' claims. However, before doing this, it is necessary to review the scientific literature to determine if other relevant studies have been conducted. This is especially important because, as mentioned before, Miss Davis does not make a serious attempt to accurately reference her statements. It is therefore quite likely that she may have failed to cite more convincing evidence. Thus, the next section of this report involves a critical review of the literature concerning selected topics presented in Miss Davis' chapter. These topics include the reported effects of lecithin and choline, vitamin B_6, magnesium, vitamin E, vitamin B_{12}, vitamin A, vitamin C, and iodine on cholesterol metabolism and atherosclerosis.

THE NUTRIENTS AND ATHEROSCLEROSIS

Introduction

The relationship between the vitamins and atherosclerosis has

received considerably more attention in Russia than it has elsewhere.

The number of studies conducted in this area in the Russian scientific

literature far exceeds those reported in Western journals. Since most

of these Russian reports are unavailable to this writer, emphasis will

be placed on what has appeared in the Western literature. Occasionally,

reference will be made to an excellent review article concerning re-

search in Russia on vitamins and atherosclerosis by Simonson and Keys,[171]

and studies summarized there will be mentioned.

LECITHIN AND CHOLINE

Since lecithin and choline are considered 'lipotropic agents' due to

their beneficial effect on some types of fatty livers, many investigators

have felt that they may play a similar role in the prevention of lipid

accumulation in the arteries. Since 1935, many studies have been re-

ported concerning this possibility. Unfortunately, most have suffered

from problems in design.

In an excellent review article concerning lipotropic agents in

arteriosclerosis, Davidson (172) points out many of the problems associ-

ated with animal studies on atherosclerosis. He emphasizes that many

factors influence the incidence and severity of atherosclerotic lesions, and as many as possible should be controlled. He states:

> In setting up an experiment the control and test groups should be of identical strain, sex distribution, age and weight. They should be carried on experiment simultaneously for the same length of time. Frequent serum cholesterol determinations should be made and the rates of weight gain should be followed. Neglect of any one of these requirements in the evaluation of a drug in the prevention or care of experimental arterio-sclerosis in rabbits leaves the results of the experiment open to question.

He adds that

> ...even with all known variables controlled there is such marked biologic variation in experimental arteriosclerosis in rabbits that it is hazardous to use less than about 20 animals for each test regimen, with an equal number of control experiments limited to feeding the same quantity of cholesterol alone.

Animal experiments have fallen into two categories: those where cholesterol and the drug have been administered simultaneously (preventive), and those where cholesterol is fed for a length of time, then withdrawn from the diet before the drug is give (curative). These two types will be considered separately.

In 1938, Steiner (173) reported that choline delays but does not prevent atherosclerosis in cholesterol-fed rabbits. Thirty-eight rabbits were fed three grams of cholesterol weekly. In addition to their normal diet, 19 were also given 500 mg. choline daily. While there were no dif-ferences in serum cholesterol levels between groups, Steiner found no gross aortic atheromata in any of the choline-treated group until the 90th day of the experiment. This is in contrast to the control group, which

showed the presence of lesions from the 40th day onwards. After 90 days, the two groups were indistinguishable. Unfortunately, Steiner does not report initial weights or rates of weight gain.

A decade later, Steiner confirmed these results (174). This time he employed 54 rabbits, and fed 3 grams cholesterol weekly. Twenty-nine were fed either 500 mg. or 1 g. of choline hydrocholride daily. Since 17 of the 29 choline treated animals failed to develop aortic lesions, as compared with only 4 of 25 in the control group, Steiner again concluded that the choline exhibited a marked protective action against the athero-genic effect of cholesterol. Steiner again does not report weight gains during the experiment and although the difference between groups appears quite large, levels of statistical significance are not reported.

In a similarly designed study, Morrison (175), dividing 81 rabbits into three groups, fed 0.5 grams cholesterol daily to all and 0.5 and 1.0 grams daily of choline to two of the groups. Whereas only 5% of the control rabbits escaped aortic atherosclerosis, 55% of the 0.5 gram choline treated group and 78% of the 1.0 gram treated group were free of lesions. This study suffers from the same problems as Steiner's.

Old hens develop atherosclerosis spontaneously, and aortic cholesterol levels have been reportedly diminished by 0.5 grams choline chloride for 77 days or less (176). Serum cholesterol was also reduced in this exper-iment. Although large sample sizes were employed (20-26 hens in each group) weight gains were again not reported.

Moses et. al. (177) reported a slight decrease in the incidence of

aortic atheromatosis in cholesterol fed (15 grams weekly), choline treated

(1 and 4 grams daily) rabbits as compared with cholesterol fed controls,

but mentioned that the average weight gain for his control group (cholesterol

fed) was 416 grams, while his experimental group averaged only a 73 gram

gain. The authors believe that the difference in incidence of lesions

may therefore be due to different changes in body weight.

Firstbrook (178), Baumann et. al. (179), and Duff et. al. (180) report

no effect of dietary choline on the development of atherosclerosis in

cholesterol-fed rabbits. Unfortunately, their sample sizes were extremely

small and thus their results are open to question.

In more recent work by Kritchevsky et. al. (181), two separate

experiments failed to show any difference in either serum cholesterol or

degree of atheromata due to choline chloride treatment. Control animals

received 2% cholesterol in the diet, while the experimental group also

received 1% choline. The experiment lasted 56 days. This negative con-

clusion is even more striking since the control group gained considerably

more weight than the experimental group. The study suffers, however, from

a small sample (roughly 8 rabbits in each group for each experiment).

Morrison and Rossi (182) have reported the curative effect of

choline on cholesterol-induced atherosclerosis in the rabbit. Twenty-one

control rabbits were fed 0.5 grams cholesterol daily for 182 days, and

then placed on a regular diet for 185 days. Morrison reported a greatly

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reduced degree of atherosclerosis in the treated group, and believes that choline causes reabsorption of aortic atherosclerosis. Statistical analysis and weight measurements were not indicated.

In a similar experiment, Steiner (183) reported similar results. Three grams cholesterol weekly were fed to rabbits for 110 days. For the next 60 days, 0.5 gram of choline daily was fed. Steiner employed only 10 rabbits in his experimental group, and does not report statistical significance. Weights are not presented.

Other studies do not confirm these positive findings. Duff et. al. (180) report no significant curative action of 3 grams choline fed daily to 11 rabbits after 3 months of cholesterol feeding in either serum cholesterol or degree of atheromata compared with 12 controls not fed choline. However, the sample was too small and the biologic variation present too large for the study to be completely convincing.

Davidson (172) reports an unpublished study by Meyer et. al. in which atherosclerosis was produced in 43 rabbits by cholesterol feeding for 107 days. The rabbits were divided into three groups. Group A was sacrificed immediately. Group B was fed a normal diet, and group C was fed 1 gram choline hydrochloride daily. Groups B and C were killed after 112 days on this regimen. In this well controlled experiment, no evidence of any effect of choline upon experimental atherosclerosis was reported.

Assuming that megadoses of choline do influence cholesterol metabolism, Chakrabarti (184) attempted to determine its mode of action. He fed choline and cholesterol to albino rats and measured serum cholesterol, fecal cholesterol, and fecal bile acids. They found that choline had a moderately hypocholestermic effect (average 52 mg% serum cholesterol compared with 87.6 mg% in cholesterol fed controls) compared with controls not receiving choline. While fecal cholesterol was unchanged, fecal bile acids increased in the choline treated group. Weight gains were measured, and the treated group gained substantially more weight than the controls. Thus, the results of the study are even more significant.

L. M. Morrison (185) reports that in 115 patients with coronary atherosclerosis given from 6 to 32 grams daily of choline, only 12 died after three years. This compares with a control sample in which 35 patients died (of 115 original participants). The two groups were matched in age. No placebo was given to the control group.

Morrison (186) also indicates that choline will decrease serum cholesterol levels and will improve the phospholipid: cholesterol ratio. Of 28 patients treated with a lipotropic preparation containing 3 grams of choline, 23 had reductions in serum cholesterol six months later. However, patients were put on a low fat diet just prior to this period. Obviously, a control group is crucial. In another report (44), in which 15 patients were put on a low-fat diet for periods up to a year prior to administration of lecithin, Morrison also shows a reduction in serum

cholesterol. Although the reduction is quite significant, the study is also uncontrolled and thus open to question.

Other reports (187, 188) in the literature have appeared concerning the beneficial effect of lecithin feeding on hypercholesteremia in human subjects, but these have involved very small samples and have not had a control group.

Jackson et. al. (188A) conducted a double-blind study involving 40 patients with symptoms of angina pectoris, giving half 3 grams choline daily and half a placebo for 4 months. He found no decrease in symptoms or number of nitro glycerin tablets taken to relieve pain during this time.

Thus, it appears that the effects of large oral doses of choline and lecithin on serum cholesterol and atherosclerosis are still controversial. Well controlled studies with a large sample are rare in the literature. While studies involving humans are few and unconvincing, those involving experimental animals are no clearer. Steiner (174) attempts to explain the conflicting reports by mentioning that dose is important. He feels that experimental atherosclerosis cannot be prevented unless the amount of choline in the diet is equal to or greater than the amount of cholesterol. However, negative reports have appeared in the literature (Baumann et. al. 179) where the choline dose far exceeded the cholesterol dose without preventing atherosclerosis. It would certainly be premature at this time to suggest that taking large doses of choline can lower serum cholesterol, or retard the progress of atherosclerosis. Although research

interest in this area has been minimal over the past 15 years, it would

seem that much more work remains to be done to establish if orally admin-

istered choline or lecithin can influence cholesterol metabolism.

Although the effects of orally administered lipotropic agents on

atherosclerosis are unclear, it has been more convincingly demonstrated

that intravenous injections of small amounts of polyunsaturated phosphatidyl

choline will markedly decrease aortic atherosclerosis in baboons (189), and

rabbits (190, 191). Intra-peritoneal injections of choline citrate appears

to be effective also (181). Friedman et. al. (35) have shown the curative

effect of four phosphatide infusions on cholesterol induced atherosclerosis

in the rabbit. It seems to this writer that this latter form of treatment

might be potentially more promising and possibly more animal and human

research should be conducted along these lines.

Vitamin B_6

The major evidence implicating vitamin B_6 and atherosclerosis has been the experimental production of arteriosclerosis in dogs (82) and rhesus monkeys (192) fed diets completely lacking in pyridoxine. Rhinehart et. al. (192) have determined that approximately 50 μg/kg body weight of pyridoxine is necessary for maximum weight gain in the rhesus monkey, a value which, if extrapolated to a 70 kg adult man, would indicate a human daily requirement of at least 3.5 mg. Since Rhinehart indicates that the average daily intake of pyridoxine is about 1.5 mg., he suggests that many Americans may be suffering from a marginal deficiency. Thus, he feels that a lack of this vitamin may play a role in the etiology of human arteriosclerosis.

Three possible mechanisms are indicated whereby a pyridoxine deficiency may exert an influence on the development of arteriosclerosis. Pilgeram (34) has suggested that animals most susceptible to atherosclerosis are least capable of converting ethanolamine to phosphatadyl choline, and he implies that adequate phosphatidyl choline is necessary for proper cholesterol metabolism. He cites evidence indicating that vitamin B_6 is necessary for the action of decarboxylase, an enzyme which forms phosphatidyl ethanolamine from phosphatidyl serine. Thus, a pyridoxine deficiency may impair phosphatidyl choline synthesis and impair cholesterol metabolism.

As pyridoxine has been implicated in the formation of arachidonate and hexaenoate from linoleate and linolenate respectively (80), an impairment

of essential fatty acid metabolism may ensue during pyridoxine deficiency. Shroeder (262) suggests that such an impairment, especially if aggravated by high saturated fat intakes, may result in intimal lesions.

Since a proliferation of the mucoprotein ground substance occuring in the intima of arteries is the characteristic lesion seen in this deficiency, Rhinehart (193) suggests that a disturbance in transamination may be responsible.

Although Rhinehart et. al. claims that lesions seen in pyridoxine deficiency are similar in pathogenesis to human aortic atherosclerosis (194) this has not been convincingly demonstrated. In B_6 deficiency, an excess of mucoprotein cementing material accumulates in the intima, often swelling into the media. Only in older, more severe lesions is lipid seen to accumulate in the sclerotic intima. Calcification is rarely prominent. The development of human atherosclerosis, on the other hand, has been shown by Holman et. al. (99) to develop early with fatty streaks, later forming into fibrous plaques and complicated lesions (calcification, etc.). The distribution of the lesions in the arteries in B_6 deficiency is also not similar to that seen in humans. Although a hypercholesteremia did develop in B_6 deficient rabbits (195), no mention of hypercholesteremia is made in the studies with dogs (82) or monkeys (192). Megadoses of vitamin B_6 (6mg/kg.) did not lower serum cholesterol in either normal or cholesterol-fed rabbits (195).

This writer feels that the evidence linking vitamin B_6 with the pathogenesis of arteriosclerosis is weak and inconclusive. Even if,

as Rhinehart suggests, many Americans are suffering from a moderate

vitamin B_6 deficiency, there is no good reason to believe that this

plays a significant role in the onset of human atherosclerosis.

Magnesium

Magnesium deficiency in dogs (196) and cholesterol-fed cebus

monkeys (197), but not in rats fed an atherogenic diet (198), resulted

in increased serum cholesterol. In carefully conducted experiments,

Vitalle et. al. (198) demonstrated that magnesium deficiency can be

induced in rats merely by feeding an atherogenic diet. Those rats fed

a normal ration of dietary magnesium (24 mg% in diet), along with cholesterol

and cholic acid, developed symptoms of magnesium depletion including hyper-

excitability, calcium deposition in the kidney, low serum magnesium, and

decreased oxidative phosphorylation of heart mitochondria. Increasing

the dietary magnesium to 192 mg% relieved these symptoms and substantially

reduced lipid infiltration of the heart valves and aorta. This reduced

atherosclerosis was not accompanied by a decrease in the hypercholesteremia.

Hellerstein et. al. (199) confirmed these findings, however, both investi-

gators noted that additional magnesium beyond the normal daily requirement

for the rat did not always have an effect on heart or lipid deposits when

the rats consumed certain proportions of protein and cholesterol/cholic

acid. Vitalle states (198) "The interrelations of the level of dietary

magnesium, protein, cholesterol, and cholate and the resultant poor growth

of animals, the low serum magnesium levels, the degree of hypercholesteremia,

the heart score and kidney lesions all require definition."

Nakamura et. al. (200) could not consistently reproduce these results

in the cholesterol-fed rabbit, but did find that a magnesium deficient diet

did accelerate the lipid deposition in the aorta in the rabbit fed an atherogenic diet.

There have been several attempts to demonstrate a correlation between serum cholesterol levels and magnesium levels. Most of these have been unsuccessful. This is to be expected in light of the fact that magnesium is an intracellular cation and therefore tissue levels are more likely to be indicative of magnesium status than serum levels (92). Thus, while Bersohn et. al. (87) found a significant negative correlation between serum magnesium and cholesterol levels between Bantus and Europeans, and also within the group of Europeans, this negative correlation was not found in careful work by other researchers (201-203). In a study taking place in Australia, Charnock et. al. (203) found no significant correlation between serum cholesterol and magnesium levels between or witin groups of aborigines, European males, European males with coronary heart disease, and young European medical students. The aborigines, which were found to have somewhat higher magnesium and lower cholesterol values in serum than the other groups, excreted less urinary magnesium in 24 hours than the other groups, suggesting that possibly their magnesium tissue saturation was not as great.

Malkiel-Shapiro et. al. (88) report treating patients successfully with intramuscular injections of magnesium sulfate. Two groups of patients have received treatment, those first seen during an acute attack of coronary thrombosis or insufficiency, and those recovering from a coronary

thrombosis or severe angina. They report that, in a trial of 22 cases, 20 showed marked improvement in their clinical condition and 14 showed a dramatic decrease in beta lipoproteins. The authors claim that the drug has 1) a vasodilating effect, 2) an analgesic effect, and 3) a lipemia clearing effect, and compare it favorably with heparin for use in cases of coronary thrombosis.

Parsons et. al. (204) also report the use of magnesium sulfate. They claim that injections will increase the phospholipid:cholesterol and alpha lipoprotein:beta lipoprotein ratios in the blood. Of 100 persons suffering from coronary heart disease (of which at least one-third were acute myocardial infarctions) treated with intramuscular magnesium sulfate, they report only one death, while 196 cases of acute myocardial infarction treated with routine anti-coagulants gave a 30% mortality.

Considering the work of Vitalle and his group cited earlier, it is evident that diet must be considered in determining the magnesium require-ment for rats. Seelig (92), in a comprehensive review concerning the human magnesium requirement, indicates that the American diet may be de-ficient and that perhaps amounts as high as 6 mg/kg should be consumed. If a moderate magnesium deficiency can accelerate the onset of athero-sclerosis and if the consumption of an atherogenic diet will raise the requirement for magnesium, then a relative lack of this mineral may pos-sibly occur and influence the course of atherosclerosis. Certainly, more work should be done concerning the role of magnesium in lipid metabolism

and atherogenesis. The interaction between diet and magnesium requirement must be better delineated. The work of Parsons (204) and Malkiel-Shapiro (88) warrant a controlled, double-blind trial of magnesium sulfate therapy to determine its efficacy in coronary heart disease. Conclusions regarding the role of magnesium in the etiology and prevention of atherosclerosis are certainly premature before further research is conducted.

Vitamin E

The belief that alpha tocopherol can conserve tissue oxygen, act
as a fibrinolytic agent, dilate capillaries, and prevent unnatural
coagulation in the tissues (109) led the Shute brothers (along with A.
Vogelsang) to propose that vitamin E may exert a beneficial pharmacologic
effect on coronary thrombosis, coronary insufficiency, coronary heart
failure, arteriosclerosis obliterans, thrombophlebitis, and intermittent
claudication (205). In 1947 W. Shute et. al. (206) first presented
clinical evidence that this therapy might be effective on the reduction
of anginal pain in coronary disease. Of 84 consecutive cases reported,
43 showed pronounced improvement, 33 partial improvement, seven slight
or no improvement, and one died. Dosage was generally between 200 and
300 mg. of alpha-tocopherol daily. Similar results were observed when
vitamine E was used to treat hypertension (207).

Since the time of these initial reports, many investigators have
attempted to confirm these results. Molotchick (208) treated three
cases of coronary disease with vitamin E and noted definite clinical
subjective improvements. It is interesting that this is the only con-
firmatory report appearing in the literature from outside the Shute clinic.

Unfortunately, however, most of the many negative findings were based
on uncontrolled studies with extremely small samples and thus were not
conclusive (209-215). For example, Baum et. al. (212) gave vitamin E to
22 patients with varying types of heart disease. Only one of 13 patients

with angina reported subjective improvement, while only three of 17 patients with symptoms of cardiac failure improved with this treatment. The authors concluded that vitamin E, in dosages recommended by Shute et. al., is of no therapeutic value.

In a somewhat better trial, Rush (216) treated 54 patients both with and without positive signs of heart disease or myocardial infarctions. All had angina. Only 7 of the 54 reported subjective improvement. In 22 patients with myocardial infarcts, only three showed beneficial changes in their electrocardiograms. To determine the likelihood that these improvements could occur spontaneously, a sample of 20 patients with coronary artery disease who did not receive any vitamin E therapy were reviewed. Twenty per cent had reported only subjective improvement; 15% showed a trend to normal in their electrocardiograms. Thus there was very little difference between the control and experimental groups.

In perhaps the best report concerning the efficacy of vitamin E therapy, Rinzler et. al. (217) conducted a controlled double-blind study on 38 patients with heart disease and chronic chest pain. Nineteen received 300 mg. alpha tocopherol daily; the rest received placebos. This dosage was used with great success in the original report by Shute et. al. Both groups were well matched with respect to critical variables. Special tests were conducted before and after the trial period to measure exercise tolerance, skeletal muscle power, and skeletal muscle endurance. Subjective reports of improvement were correlated with these more objective measures.

After approximately 16 weeks of medication, 37% receiving vitamin E and 27% receiving placebo reported subjective improvement. The placebo group showed greatest improvement on the exercise tolerance test, while there occured no difference between the groups on the other tests. The patients who indicated improvement with the vitamin therapy did not show a corresponding improvement on the objective tests. The authors conclude that they cannot confirm the reported benefits of alpha tocopherol in cardiac pain.

Other reports have indicated that vitamin E is not effective in the treatment of thrombophlebitis and thromboembolic states (218), nor in the treatment of thromboangitis obliterans and leg ulcers (219). The only positive trials have been limited largely to vitamin E therapy and intermittent claudication (220). Small but well-controlled studies (221, 222) have indicated a therapeutic effect. These reports need to be confirmed with larger samples.

Vitamin C

High intakes of vitamin C have been recommended for the treatment

of atherosclerosis and hypercholesteremia in Russia for quite some time (130).

This mode of therapy has been backed by numerous investigations reported

in the Russian literature. Summarized by Simonson and Keys (171),

these reports include clinical trials where from 500 to 1,000 mg. of

ascorbic acid is administered to small numbers of patients. Control groups

are very rarely employed in these studies, and statistical tests of signi-

ficance are not reported. However, Sedov, in 1952, administered from 500

to 1,000 mg. ascorbic acid daily to 106 patients for twenty to thirty days.

Before the treatment 23% of the patients were stated to have had serum

cholesterol values over 250 mg.%, but after the treatment only 2.3% had

such high values. Simonson and Keys found this change to be highly sig-

nificant. Only patients with initially high values were effected.

Intravenous ascorbic acid is also thought to lower the serum cholesterol,

although there seems to be some dispute concerning the rapidity of action.

Lobova found an increase in alpha and a decrease in beta lipoproteins upon

a daily intravenous dose of 1,000 mg. in most patients.

Russsian researchers have also extensively employed experimental animals

in their studies. Myasnikov (129) gave between 100 and 200 mg. of ascorbic

acid to rabbits receiving an atherogenic diet. A control series did not

receive this supplement. Thirty-five rabbits were employed in this study.

After 100 days, serum cholesterol levels increased by 238% in the control

group, but by only 116% in the group supplemented by vitamin C. The treatment group also had considerably less lipid deposition in the aorta than the controls.

There have been several attempts to corroborate this work in the Western literature. Anderson et. al. (223) gave 1,000 mg. ascorbic acid to 24 patients on rigidly fixed diets in alternating periods of three to four weeks at a time. No significant effect was observed. Since the patients in this study were normocholesteremic, this work does not contradict Sedov's results. Hanck (224), however, did find a hypocholesteremic effect of massive doses of ascorbic acid given to middle aged normocholesteremic men previously well supplied with dietary vitamin C.

Samuel et. al. (225) gave from one to six grams of vitamin C to 14 patients, all of which had average serum cholesterol concentrations of 300 mg.% or higher. After five to 16 weeks, only one patient showed a marked decrease, while two patients showed improvement of borderline statistical significance. Unfortunately, this study has a small sample size, is uncontrolled and entails no supervision of diet.

Spittle (226) found a slight increase in serum cholesterol after giving 58 patients one gram daily ascorbic acid for six weeks. In 25 patients with atherosclerosis (mean serum cholesterol prior to therapy - 242 mg.%), this rise was also noted. On the other hand, Sokoloff et. al. (227) noted a slight hypocholesteremic effect of 1.5 to 3.0 grams ascorbic acid daily to 60 patients with pronounced hypercholesteremia and/or

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cardiac disease. In neither study was a control group reported, nor was their any apparent attempt to monitor the diet or measure weight gain.

Although Samuel et. al. (225) found no effect on serum cholesterol after intravenous administration of vitamin C in two hypercholesteremic patients, Cortinovis et. al. (228) indicates that this type of therapy does have a slight lowering effect on hypercholesteremic persons, but not in normals. This effect is seen after one hour. C. Silenzi et. al. (229) have also found an increase in the alpha/beta lipoprotein ratio one hour after parenteral injection of ascorbic acid. After three hours, lipoprotein levels were back to normal.

These clinical studies present a very confusing picture concerning the effectiveness of this type of therapy. Unfortunately, experiments in animals do not clarify the issue to any great extent.

Nambisan et. al. (230) fed 5 mg. ascorbic acid per 100 grams of body weight to weanling rats fed a normal diet for one month. Compared with controls, these supplemented rats showed a sifnificant decrease in serum cholesterol, phospholipids, and triglycerides, also a great decrease in cholesterol of the aorta. Controls were not pair-fed with the treated group in this study.

Most of the other studies illustrating the pharmacologic effect of vitamin C use the rabbit fed a cholesterol enriched diet. The effect of ascorbic acid on the resulting hypercholesteremia and incidence of ather-osclerotic lesions is then reported. Unfortunately, none of the investigators

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pair feed their control and experimental groups, and weight data are generally not presented. This information is certainly pertinent in order to determine the effect of the treatment itself on atherogenesis. Zaitsev (231) administered 200 mg. per kg. cholesterol daily to 23 rabbits for 45 days. Eleven of these also received ascorbic acid in a dose of 0.1 gram per kg. body weight per day. Although there was no real change in serum cholesterol, the cholesterol concentration of the aorta in the ascorbic acid treated group was greatly reduced -- nearly normal levels.

Sokoloff (227) presents epidemiological evidence that alimentary lipemia might play a role in the etiology of atherosclerosis. Lipoprotein lipase (LPL) is capable of hydrolysing the triglycerides in the chylomicra and therefore plays a primary role in clearing turbid plasma. Sokoloff reports that feeding rabbits an atherogenic diet (up to 100 mg./kg. cholesterol daily) severely reduced LPL levels in the blood. However, administering 150 mg. per kg. of ascorbic acid restored these levels almost to normal values. After eight months the rabbits fed both cholesterol and ascorbic acid had reduced whole blood cholesterol (308 mg.% as compared with 1234 mg.% for the cholesterol fed group) and triglyceride concentrations. Histopathologic findings demonstrated a reduced incidence of atheroscler-osis in the ascorbic acid treated group. This study employed an extremely large number of rabbits (60 in each group) and appears to be carefully con-ducted. However, one point difficult to explain is the extremely low standard deviations found in cholesterol measurements. In a series of

only five rabbits, for example, standard deviations of the mean were often reported as low as one to two percent. Considering the normal biologic variation in serum cholesterol between animals, such uniformity in a small group is difficult to understand. Sokoloff also presents data to indicate that ascorbic acid has a hypocholesteremic effect on cholesterol fed rats.

In a similar study, Datey et. al. (232) reported that ascorbic acid inhibited the development of atherosclerosis. Seventeen rabbits were fed a highly atherogenic diet (26% hydrogenated fat and 4% cholesterol). Twenty-two of these also received 200 mg. ascorbic acid daily. After eight weeks serum cholesterol was greatly reduced in the ascorbic acid group. Twenty of these animals had normal aortas upon autopsy, whereas only eight of the cholesterol fed control rabbits were free of lesions.

Davis et. al. (233) also claims a preventive role of ascorbic acid when administered to rabbits with experimentally induced atherosclerosis. These workers produced aortic sclerosis through the combined injections of epinephrine and thyroxine. Doses of 500 mg. per kg. of ascorbic acid were most effective in reducing the incidence of these lesions. Inositol was completely ineffective.

This writer has been able to find only three reports indicating that vitamin C is without effect on limiting the onset of experimental athero-sclerosis. Chakravarti (234) et. al. injected 50 mg. of ascorbic acid intramuscularly to rabbits fed 0.5 grams cholesterol per day. Control

rabbits received the cholesterol only. After 12 weeks, the experimental group showed only an insignificant reduction in serum cholesterol, and a similarly small decrease in atheroma of the aorta. However, since each group consisted of only six rabbits, the validity of these negative findings can be questioned.

The same criticism can be applied to the work of Flexner et. al. (235), who divided 49 rabbits into so many experimental groups that only three to six rabbits received each treatment. All rabbits received 3 grams cholesterol weekly. Five, four, and three rabbits received 5, 50, and 10 mg. ascorbic acid respectively. After experimental periods of 101 and 60 days, no significant differences in blood cholesterol were observed. Ascorbic acid therapy did not appear to consistently reduce the cholesterol content of the aorta.

Pool et. al. (236) found no effect of 5g./kg. body weight of ascorbic acid on either hypercholesteremia or atherosclerosis of the aorta in rabbits fed an atherogenic diet for 16 weeks. This was also a small study, as both experimental and control groups contained only five rabbits each.

In general, these experiments would seem to indicate that large doses of vitamin C can affect lipid metabolism and influence the onset of atherosclerosis. Most of the doses used have been extremely large (corresponding to between 5 and 10 grams daily for a 70 kg. man), especially considering that the rabbit and rat can sythesize their own ascorbic acid. This writer feels that the therapeutic effect of this vitamin on experimental

atherosclerosis should be confirmed by better controlled studies, and, if possible, a dose-response relationship worked out for different degrees of atherogenic diets. More work should also be done in guinea pigs, which cannot synthesize their own ascorbic acid, and thus more nearly approximate man in this respect.

In 1953, Willis (237) demonstrated atheroscerotic lesions in the aorta in guinea pigs fed a scorbutogenic (but not necessarily atherogenic) diet. These lesions took 15 days to develop. Willis claimed that these lesions were identical to those seen in human atherosclerosis. He postulates that an ascorbic acid deficiency induces a depolymerization of the intercellular glycoprotein ground substance of the arterial intima. Stainable lipid is then deposited in this altered ground substance. Capillary invasion of the intima and subsequent hemorrhaging then occurs. Thrombosis may then occlude the already narrowed artery. He reported (237A) that ascorbic acid repletion can reverse this process.

Willis et. al. (238) also demonstrated that the ascorbic acid content of the aorta is often extremely low in patients suffering from chronic disease, and tends to be less in those areas that seem to be most prone to atherosclerosis (aorta as compared with carotid sinus and internal carotid arteries). Shaffer (239) reviews the evidence for the role of ascorbic acid in atherosclerosis and concludes there is "a basis for the presumption of deficiency in ascorbic acid in persons to be a contributing factor in the development of myocardial, aortic, and cerebral atherosclerosis."

That an acute vitamin C deficiency severely affects lipid metabolism

has been demonstrated by Banerjee and associates in the guinea pig (240, 241)

and rhesus monkey (242). However, neither Ginter et. al. (243) nor Gore

et. al. (244) could produce atheromatous lesions in acutely scorbutic guinea

pigs and thus could not confirm the work of Willis. To study this problem

further, Ginter has favored a chronic vitamin C deficiency, rather than

acute scurvy, as an experimental model, since this more closely approaches

the present nutritional status in civilized countries (243). He has shown

that guinea pigs maintained on 0.5 mg. vitamin C per day (as compared with

controls fed the normal requirement of 5 mg./day) have higher serum cholest-

erols and oxidize less cholesterol to bile acids (245). This chronic

hypovitaminosis group shows similar weight gains as the controls. Moreover

he has shown that guinea pigs fed an atherogenic diet have decreased

tissue levels of vitamin C and excrete more vitamin C in the urine, com-

pared with controls fed a normal diet with the same amount of ascorbic

acid. Rabbits and rats, able to synthesize ascorbic acid as necessary,

showed tissue levels of ascorbic acid to be greater in cholesterol fed

groups (246). Ginter et. al. (247) further demonstrated that guinea pigs

fed a large dose of ascorbic acid (50 mg. per day) plus an atherogenic

diet showed tissue concentrations of ascorbic acid similar to control

animals fed a diet containing 5 mg. vitamin C per day but without chol-

esterol. Animals receiving this normally required dose with cholesterol

showed strikingly less ascorbic acid concentrated in the tissues. Tissue

cholesterol concentrations appeared to be negatively correlated with levels of vitamin C intake.

This work by Ginter and associates indicates that an atherogenic diet can increase tissue requirements for ascorbic acid. If this increased requirement is not met, then the cholesterol concentration will increase in some tissues. It is interesting to note that after feeding an atherogenic diet (0.3% cholesterol) for 139 to 142 days, Ginter et. al. (247) found that histologic differences in the aorta between guinea pigs fed 50 mg. ascorbic acid per day and those fed 5 mg. per day were not very marked. However, more numerous lesions were found in the group fed 0.5 mg. per day.

To study the effect of ascorbic acid on cholesterol levels in humans, Ginter et. al. (248) gave 300 mg. supplements to 24 persons suffering from a seasonal deficit of vitamin C. After administration for 47 days, serum cholesterol levels were slightly, but significantly reduced compared with 18 controls given a placebo. The effect of ascorbic acid was most pronounced in persons with hypercholesteremia.

Thus it appears that ascorbic acid plays an important role in cholesterol metabolism, and a chronic deficiency may be one factor involved in hypercholesteremia. A diet high in fat and cholesterol appears to significantly increase the requirement for this vitamin, and thus a moderate deficiency may be induced with previously normal intakes. Such a deficiency may play some role in the pathogenesis of atherosclerosis,

although, to what extent is at present uncertain. If such an increased requirement exists, pharmacological doses of the vitamin may be of value in lowering serum cholesterol and affecting the onset of atherosclerosis. However, the beneficial effect of large doses of vitamin C beyond fulfilling this requirement has not been conclusively established.

Iodine

Iodine has traditionally been used in the treatment of atherosclerosis although without convincing results (249). Since it is well known that hypothyroidism is associated with hypercholesteremia and increased incidence of atherosclerosis (249), the rationale behind iodine therapy may have originally be centered around attempts to increase thyroxin or thyroxinlike substances. There have been a few carefully controlled studies appearing in the English literature, concerning its effect, and these will be outlined below.

Iodine has been shown not to reduce cholesterol levels in normocholesteremic states. This has been demonstrated when iodine was added in large amounts to the normal diet of the dog (250), rat (251), and rabbit (249). Several workers have also reported that iodine exerts no beneficial effect on the hypercholesteremia and atherosclerosis resulting from atherogenic diets. Dauber et. al. (252) fed 0.5, 1.0, and 2.0 percent cholesterol to the diet of chicks. These workers found that the addition of doses of potassium iodide varying from 800 to 1,500 mg./kg. per day did not impede the development of atherosclerotic lesions of the aorta. However, with a dose of 2,000 mg. per kg. per day in animals receiving 1 percent cholesterol, some protective action was observed. Serum cholesterol levels were somewhat greater in those groups treated with iodine.

Moses et. al. (253) fed a highly atherogenic diet to rabbits (5 grams of cholesterol three times a week). Three hundred twenty-five and 20 mg.

of iodine was also administered to two different groups. The iodine

treated and the control groups all had about the same degree of aortic

atheromata after seven weeks. Weight gains were recorded, and the rabbits

fed 325 mg. of iodine plus cholesterol gained considerably more weight

than controls. This is unfortunate, since there actually was a slight re-

duction of atheroma in this group. It is surprising that although these

authors seemed to appreciate the effect of weight gain on the incidence

of atherosclerosis, they did not think to pair-feed their experimental

and control animals.

As early as 1933, Turner (254) reported a remarkable beneficial

effect of iodine on experimental atherosclerosis. Twenty-one control

rabbits fed 3 grams of cholesterol per week had an average blood choles-

terol of 520 mg% after three months. Fourteen showed gross atheroscler-

otic lesions. However, in 12 rabbits fed three grams potassium iodide

per week, only one showed signs of atherosclerosis after three months.

Average serum cholesterol was 183 mg.%. Moreover, he found that this

protective action of potassium iodide disappears when the thyroid glands

are removed (255).

Brown et. al. (249) also demonstrated this protective effect. In

order to determine a minimum dosage level, they administered 0, 1, 10, 20,

and 40 mg. potassium iodide daily to groups of rabbits on a mildly athero-

genic diet (maximum 400 mg. cholesterol daily). Thyroidectomized animals

also received these diets. It appeared that serum cholesterol decreased

as the dose of potassium iodide increased, and 40 mg. reduced serum choles-

erol levels to those seen in animals on a non-atherogenic diet. Interest-

ingly enough, as little as 1 mg. of potassium iodide significantly decreased

serum cholesterol in the thyroidectomized rabbits treated with cholesterol.

Therefore, these authors conclude, contrary to Turner (255), that the

effect of iodide on cholesterol metabolism is independent of the thyroid

gland.

Brown et. al. also attempt to explain the conflicting reports in the

literature. They mention that the amount of cholesterol in the diet is

important, since "iodide can only give protection when the amounts of

cholesterol are not excessive. Usually no protection has been reported

when rabbits were fed over 500 mg. a day." Therefore, according to these

authors, the study by Moses et. al. employed too great a dose of cholesterol.

Since chickens develop severe atherosclerosis on minimum amounts of choles-

terol, these writers feel that this species is not a good model to use

for these studies.

Pitel (136) reported a significant drop in serum cholesterol after

administering iodine to 74 patients. Unfortunately, this study is dif-

ficult to interpret since Pitel placed patients on a low fat diet and yet

did not report data for his control group.

Although the evidence supporting a favorable effect of iodine on ex-

perimentally induced atherosclerosis is not overwhelming, it is certainly

encouraging enough to warrant further study. It is therefore surprising

that so few reports concerning this topic appear in the medical literature.

Hopefully, other workers will attempt to confirm the positive findings

reported thus far. Particularly important will be attempts to establish

the mechanism of its action. At the momment, conclusions concerning the

extent and nature of iodine's therapeutic effect are premature.

Vitamin A

Very few studies have appeared in the English literature concerning the role of vitamin A in atherosclerosis. Kinley and Krause (124) reported significantly decreasing the cholesterol levels of eight hypercholesteremic persons with the administration of 100,000 IU of vitamin A acetate daily for six months. Normocholesteremic individuals were not affected. Unfortunately, figures for the control group aren't reported and, since a restriction in fat intake was reported at the start of the study, a decrease in serum cholesterol was therefore to be expected.

Pallotta et. al. (123) repeated the above study with 24 geriatric patients. Here, the average serum cholesterol level of the experimental group was not significantly affected, however, the average serum phospholipid levels did increase significantly over that of the control group.

In the chick, Beeler et. al. (256) found that administration of 3,000 to 5,000 IU daily of vitamin A sharply reduced the hypercholesteremia produced on a high-fat diet containing 1% cholesterol. The severity of atherosclerosis was also markedly lowered. This hypocholesteremic effect of vitamin A was eliminated when sodium glycocholate was added to the diet. Unfortunately, bile acid and cholesterol excretion in the feces were not measured in this study. Although the number of chicks in each group checked for atherosclerotic lesions was small, the decrease in intimal area involved in these lesions in the group fed vitamin A appeared to be very great (about one eighth as much as the controls). There were no

significant differences in weight gain between the two groups.

Krause et. al. (257) observed less free cholesterol deposited in arterial tissues of dogs fed 5,000 IU of vitamin A and an atherogenic diet than in a similar group fed only the atherogenic diet. However, cholesterol esters and total lipid deposition was greater in the vitamin treated group in these tissues and no difference in serum cholesterol levels was observed between groups.

In a less ambiguous study, Oppenheim et. al. (258) found no effect of large doses of vitamin A on serum cholesterol levels of normal rabbits, nor of cholesterol contents of the blood of cholesterol-fed rabbits. Fifty thousand USP units of vitamin A three times weekly were given to the treated rabbits. Dietary cholesterol consisted of one gram fed three times weekly. The experimental period lasted 14 weeks. Those rabbits (19 in this group) fed both cholesterol and vitamin A showed no change in serum cholesterol or phospholipid, and no change in concentration of aorta cholesterol.

Bonner et. al. (259) also could not confirm positive reports concerning the action of vitamin A on serum cholesterol. These workers gave either rabbit chow, chow plus 200 mg. cholesterol, or chow plus 200 mg. cholesterol plus 25 million units of vitamin A acetate to rabbits for one year. There were ten rabbits in each group. Although the vitamin treated group showed a mildly reduced serum cholesterol and degree of atheromata compared with the cholesterol-only group, the results were not significant.

From these studies, no definite conclusion concerning the role of vitamin A in atherosclerosis can be reached. In the chick vitamin A has been shown to counteract the onset of atherosclerosis; this study awaits confirmation from other investigators. At the moment, no clear evidence exists which suggests that large doses of vitamin A (which can be toxic) will be helpful in treating hypercholesteremia or atherosclerosis in humans.

Vitamin B_{12}

Although Russian workers have taken a considerable interest in the role of vitamin B_{12} in atherosclerosis, few reports appear in the Western literature. When large doses of vitamin B_{12} have been administered to patients with coronary heart disease, both Lukomskii and Motovilova (as described by Simonson and Keys - reference 171) noted decreases in serum cholesterol of from 18 to 23 mg. percent. Simonson and Keys found these changes to be statistically significant. Patients also reported subjective improvement and some showed improved or normal electrocardiograms.

Large doses of vitamin B_{12} fed to rabbits with 200 mg. cholesterol daily appeared to reduce hypercholesteremia and delay atherogenesis. Vitamin B_{12} therapy also appeared to speed the reduction of hypercholesteremia after it had been induced by a high cholesterol diet. On the basis of the results of these and similar studies, a leading Russian medical scientist, Miasnikov, recommends the use of vitamin B_{12} in a dosage of 0.6 mg. every second day for two to four weeks for prevention and treatment of ather- osclerosis, though he indicates that clinical experience is currently too limited to permit a conclusive evaluation.

In 1957, Chakravarti et. al. (234) fed 12 rabbits 0.5 grams cholesterol daily for 12 weeks. Six were also given intramuscular injections of 10 μg. vitamin B_{12}. While total cholesterol in the B_{12} injected group was not greatly reduced, the amount of cholesterol esters had decreased such that the free to total cholesterol ratio was greatly increased. A decrease was

also noted in the cholesterol to phospholipid ratio. Less atheroma of the aorta was seen in the vitamin-treated group (22.5% mean lesion per aorta compared with 36.6% in the group fed only cholesterol). Due to the small number of rabbits employed in this study, the results reported may not be significant (statistical tests were not presented). The small differences reported between groups may also be due to differences in weight gain (not reported).

Nath et. al. (260) repeated the above study, using five rabbits per group and continuing the experiment for ten weeks. The same dosages of cholesterol and vitamin B_{12} were employed. They found that marked decrease in total cholesterol occured in the B_{12} treated group, however, the free to total cholesterol level was unchanged. The cholesterol to phospholipid ratio was again greatly decreased. No significant differences in weight gain were observed between the two groups. It is unfortunate that larger numbers of animals were not used and that appropriate statistical techniques were not employed in either study.

Attempts to delineate a possible mechanism behind this vitamin's mode of action have been highly conceptual. Nath et. al. (260) mention that vitamin B_{12} is associated with methionine and choline metabolism. Since both of these agents are termed 'lipotropic', they may have some beneficial effect upon lipid metabolism. In support of this, these workers found over three times as much methionine in the liver in B_{12} treated rabbits compared with rabbits fed either a normal or cholesterol diet without this vitamin. However, no decrease in liver fat was observed in the vitamin treated group.

The effect of vitamin B_{12} on bile acid excretion was examined by

Nath et. al. (122) and Banerjee et. al. (261). Nath et. al. found that

injections of 5 ug. vitamin B_{12} daily per 100 grams to rats fed a diet

high in saturated fat significantly lowered total plasma cholesterol and

increased bile acid excretion. Control rats fed only the high fat diet

had average daily excretions of cholic and dihydroxycholanic acid of

.372 and .414 mg. Serum cholesterol was 205 mg.%. The group treated

with the vitamin excreted .760 and .648 mg. daily of these two bile acids.

Average serum cholesterol was reduced to 138 mg.%. Although a statisti-

cal analysis was not presented, these differences appear to be highly

significant based upon the indicated standard deviations.

In a similar study, Banerjee et. al. (261) induced a hypercholester-

emia through feeding a 1% cholesterol diet to rats. He found that orally

administered vitamin B_{12} (100 ug. of vitamin B_{12}/100 grams of diet) markedly

lowered blood cholesterol, increased the fecal excretion of bile acids,

and did not change the fecal excretion of cholesterol. The cholesterol

content of the liver was also greatly reduced. The authors suggest that

"the cholesterol lowering effect of vitamin B_{12} may be attributed to in-

creased conversion of cholesterol into bile acid which is excreted in

the feces."

Although this writer has been unable to find negative reports con-

cerning this vitamin's action on hypercholesteremia and atherosclerosis

in the literature, positive reports are too few to permit conclusions.

The work presented here indicates that B_{12} therapy can reduce serum cholesterol and increase bile acid excretion, however, the four original papers reviewed come from only two separate laboratories. Hopefully, this work will be confirmed by others and perhaps eventually extended to man.

Conclusion and Summary

The relationship between nutrition and atherogenesis is extremely complex. Deficiencies of pyridoxine, ascorbic acid and magnesium all seem to either result in or promote the development of atherosclerotic-like lesions in experimental animals. The extent to which these lesions are similar to those seen in the human is still an open question. Some investigations have indicated that large doses of choline or lecithin, ascorbic acid, vitamin A, vitamin B_{12} and iodine can partially prevent or cure experimentally-induced atherosclerosis. With the possible exception of vitamin B_{12} (where too little work has been done) none of these claims have been uniformly confirmed. However, the bulk of evidence seems to suggest that pharmacologic doses of ascorbic acid and iodine can hinder the onset of experimental atherosclerosis, while vitamin A cannot. Reports concerning choline or lecithin have been more contradictory. Only poorly designed studies have been conducted thus far in humans.

It appears that the requirement for ascorbic acid, and perhaps magnesium, increase when animals are fed an atherogenic diet. In these two instances, increased intakes have been necessary to maintain appropriate tissue concentrations and reduce the induced atherosclerosis in some cholesterol fed animals. The effect of these nutrients on lipid metabolism still requires definition.

Large doses of vitamin E are without effect in treating ischemic heart disease. The only support for its therapeutic value comes from

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one investigator, while numerous other workers have been unable to confirm his results.

It is unfortunate that most studies investigating the effect of the above nutrients on hypercholesteremia and atherogenesis are poorly designed and thus are difficult to interpret. There is also the possibility that well controlled studies may not have been reported because negative results were found which were not thought worthy of publication. These factors color the perspective of one trying to determine the role of these nutrients in the pathogenesis of atherosclerosis.

Closing Remarks

From the above literature review, several points become clear concerning this chapter of Adelle Davis' book, <u>Let's Get Well</u>. It is apparent that Miss Davis could have done a much better job of referencing her book. Her policy has been to quote some relevant articles along with several which aren't relevant, and then to subtly exaggerate the facts to make her 'expose' appear more dramatic. The irrelevant references which she cites makes it seem that all her statements are documented by many different sources.

In fact, Miss Davis could have found support in the scientific literature for most of her claims concerning the effects of the nutrients she mentions. There are ample studies reported which back her up; she mentions only a few. If she had found the others, then the false referencing would not have been necessary.

Therefore, although her references often do not lend credence to her statements, there is a measure of truth in much of what she says. However, this truth is often coupled with subtle exaggerations. For example, she will say that a nutrient such as iodine (p. 56) or magnesium (p. 54) will prevent experimentally produced atherosclerosis. The facts are, however, that supplemental doses of these nutrients have limited (not prevented) induced atherosclerosis in certain situations. Adelle's literary style is one which makes qualitive differences appear absolute and specific results appear general.

As has been mentioned before, research concerning the effects of the nutrients which Miss Davis cites on hypercholesteremia and atherosclerosis have, in general, not produced conclusive results. Therefore, it is certainly premature to recommend these nutrients to individuals for their possible beneficial impact on lipid metabolism and coronary heart disease. The fact that Miss Davis does make such recommendations is unfortunate, regardless of how well she is able to document her assertions.

Let's Get Well is a book intended for the general public -- for those concerned about nutrition and their health. This unassuming audience should be exposed to information which is widely held to be correct and has been conclusively demonstrated in different laboratories. If a controversial point is raised, it should be stated as such. However, Adelle Davis presents many theories, based on inconclusive and conflicting research, which she articulates as proven fact. Even a well-trained nutritionist would be hard put to separate fact from fiction. This deception, resulting from statements which are often only slightly inaccurate, is unpardonable when published in the mass media.

Dietary and Serum Cholesterol

As is evident from her section entitled "Low-fat and Low Cholesterol

Diets," Adelle Davis feels that limiting cholesterol intake will not re-

sult in lower serum cholesterol values. In fact, she states:

> Diets low in cholesterol have...achieved exactly the
> opposite of what was hoped. Such diets throw the liver into
> a frenzy of cholesterol-producing activity, causing the amount
> in the blood to increase. 51, 60, 74, 149

The references she cites here do not support her claims (see pages

20-21 of this report). However, since dietary cholesterol restriction

is currently often considered important for those with hypercholesteremia,

this writer thought it might be interesting to briefly review experiments

reported in the scientific literature concerning the effect of dietary

cholesterol on serum cholesterol levels.

Until 1957, the general concensus among major investigator was that,

within a considerable range, dietary cholesterol was without effect on

serum cholesterol levels. There appeared to be no correlation of dietary

cholesterol and serum cholesterol values either within or between a coro-

nary disease group and a control group (263), and various crystalline

cholesterol supplements added to diets did not seem to raise serum lipid

levels (264-266) over short intervals of time. When extra egg yolk was

added to diets, reports were conflicting. Keys et. al. (267) found no

effect on serum cholesterol in six subjects when egg yolks containing 500

to 600 mg. of cholesterol were added to a low fat, zero cholesterol diet

(rice-fruit diet). Mayer et. al. (268) found similar results by adding
800 mg. cholesterol to a low cholesterol diet (containing 150 mg. cholesterol).
However, Messenger et. al. (269) reported that feeding egg yolk supplements
(3.75 g. cholesterol) greatly increased serum cholesterol levels, whereas
feeding crystalline cholesterol did not.

Unfortunately, most of these studies used small samples and were poorly
controlled. Often the cholesterol containing substance (usually egg yolk
or crystalline cholesterol mixed in a fat) was simply added to the diet,
and therefore the calorie and fat content of the control and experimental
diets were not uniform. If crystalline cholesterol was employed, generally
no attempt to approximate the amount absorbed was made. Even if total
calories and percent fat calories ingested in both control and experimental
groups were kept standard, the iodine values of the ingested fat were often
different and this factor also will affect serum cholesterol levels. Al-
though these problems rendered the above studies inconclusive, certain
investigators (263, 267) quickly reached the conclusion that serum
cholesterol is essentially independent of a wide range of cholesterol
intake.

Interestingly enough, almost every study reported in the literature
since 1959 demonstrates that changes in dietary cholesterol will affect
serum cholesterol levels, contrary to these earlier reports. For example,
Beveridge et. al. (270, 272) fed a homogenized formula fat-free diet to 167
students in two separate studies. These workers then substituted a low-

cholesterol butter-oil fraction for 30% of calories at the expense of

an equicaloric amount of carbohydrate. By eight days, they found a sig-

nificant 10% increase in serum cholesterol values. However, if varying

amounts of cholesterol were added to the butterfat fraction before substi-

tution in the diet (0 to 1600 mg. cholesterol per 950 calories), then serum

cholesterol appeared to increase by as much as 60% in the same time interval.

Those eating the butter-oil diet without added cholesterol had the smallest

increase in serum cholesterol values. From these studies, the authors con-

cluded that serum cholesterol increases as a function of dietary cholesterol

up through intakes of 634 mg. per day. Beyond this amount, the dose-response

curve is flat.

Keys et. al. reversed their earlier position (267) concerning the in-

ability of dietary cholesterol to alter serum cholesterol values. In a

study involving 22 men, this group carefully varied the cholesterol content

of the diet (while keeping other dietary factors as constant as possible)

and found that the serum cholesterol appeared to be a linear function of

the square root of the cholesterol in the diet. They derived the following

equation:

$$\triangle \text{chol.} = 1.5 \ (Z_2 - Z_1)$$

where $\triangle$chol. is the change in serum cholesterol from period
    two to period one, measured in mg.%
Z_2 is the square root of dietary cholesterol expressed in mg.
    per 1,000 calories of diet ingested in period two.
Z_1 is the same as above, ingested in period one.

Applying this equation to the combined data from their own and other

studies reporting similar findings (Beveridge et. al. (271), Steiner et. al. (273), Conner et. al. (274), Erickson et. al. (275), Keys et. al. (276) found a correlation of 0.95 between the observed serum cholesterol values and those predicted by the equation.

On the other hand, Hegsted et. al. (277) observed the effect of various types of dietary fat on serum cholesterol and concluded that the following relationship holds:

$$chol. = 2.16\triangle S - 1.65 \triangle P + 6.77 \triangle C - 0.53$$

where S and P are percentages of total calories from glycerides
        of saturated and polyunsaturated fats, respectively
C is the dietary cholesterol measured in decigrams per day.

Therefore, this group felt that linear relationship existed between serum and dietary cholesterol, and that for every 100 mg. cholesterol per day added in the diet, serum cholesterol would increase by 6.8 mg.%, other factors remaining constant.

Keys et al. (276) had earlier derived a different prediction equation:

$$chol. \quad 1.3 \ (2 \triangle S' - \triangle P) + 1.5 \ (Z_2 - Z_1)$$

where S' is the percentage of total calories provided by gly-
        cerides of saturated fatty acids, omitting stearic acid.

Keys et. al. (276) then compared both equations to the data which this same group had examined earlier (278). They found that their own prediction equation fit the data much better than that of Hegsted et. al., primarily because of the error introduced by the linear cholesterol term.

If the term $1.5(Z_2 - Z_1)$ does accurately express the effect dietary cholesterol will have on serum cholesterol levels, then perhaps some of

the negative results from earlier studies can be better understood. For example, Moses, et. al. (264) fed two grams of cholesterol incorporated in candy daily to pregnant women. Since the women were already eating diets rich in cholesterol, the difference in the square roots of the two cholesterol intakes is not as large as if the women were switched from a moderately high cholesterol diet (400 to 600 mg. per day) to one free of cholesterol. Considering also that large amounts of dietary cholesterol are likely to be excreted unless presented with adequate amounts of fat, it is not difficult to see why such studies did not yield positive results. Keys et. al. (276) calculate that if dietary cholesterol is reduced from 300 to 150 mg. per 1000 calories-resulting in a decrease in serum cholesterol of 7.5 mg.% - 50 subjects would be necessary before the observed difference would be significant statistically. Since much smaller samples were usually employed in earlier studies, similar small but important differences probably went unobserved.

Based on these more recent studies, there now appears to be little doubt that dietary cholesterol does influence serum cholesterol levels. However, the practicality of appreciable serum cholesterol reduction through restriction of dietary cholesterol intake alone can be questioned, since unless the effort to reduce cholesterol in the diet is heroic, the net change in the serum will be small. Therefore, it can be concluded that, while a limitation of dietary cholesterol is prudent for an individual with hypercholesteremia, it is perhaps more important that the amounts of saturated and unsaturated fats consumed be regulated appropriately.

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